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<b>(21) International Application Number:</b> PCT/EP93/01277 <b>(22) International Filing Date:</b> 17 May 1993 (17.05.93) <b>(30) Priority data:</b> 9210947.9                      22 May 1992 (22.05.92)                      GB <b>(71) Applicant (for all designated States except US):</b> THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> GALLEY, Edward [GB/GB]; COOPER, Michael, David [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB). <b>(74) Agent:</b> SMITH, Elizabeth, Jane; The Boots Company plc, Patents Department, R4 Pennyfoot Street, Nottingham NG2 3AA (GB).		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> ORAL HYGIENE COMPOSITION  <b>(57) Abstract</b>  An oral hygiene composition comprises an effective amount of an antimicrobial agent in the form of a particulate non-ion-exchanging support material combined with a metal source providing antimicrobial metal ions in use. Preferably the antimicrobial agent is particulate titanium dioxide coated with silver chloride.		

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Oral hygiene composition

The present invention relates to an oral hygiene composition providing sustained antimicrobial action. There is also provided inter alia the use of such a composition in the treatment or prevention of dental caries or gingivitis and in the cleansing of the mouth for cosmetic purposes.

The term 'oral hygiene composition' as used herein indicates a formulation for use in any form of oral hygiene or dental treatment and includes inter alia dentifrices, mouthwashes, toothpowders, chewing gums, lozenges, mouthsprays, flosses, denture cleansing formulations, tooth paints and glass ionomer cements.

The use of antimicrobial agents in oral hygiene compositions is well-known in the art. Typically, the anti-microbial agent is an organic species such as chlorhexidine, bromochlorophene, cetyl pyridinium chloride or benzethonium chloride. These agents are known to be effective against the microorganisms associated with dental caries and gingivitis, such as the bacteria *Streptococcus mutans* and *Streptococcus salivarius*, and the fungus *Candida albicans*.

It is also known to use metal ions, such as silver, copper and zinc ions, as antimicrobial agents in medicine, dentistry and in water purification.

In an oral composition, however, such organic and inorganic antimicrobial agents present the problem that they are readily displaced from the mouth, and thus from their intended point of action. For example, they may be washed out of the mouth by saliva or adsorbed onto food at mealtimes. Accordingly, their oral

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antimicrobial action can rarely be sustained over long periods.

The present invention seeks to solve this problem by providing an oral composition comprising an antimicrobial agent with a tendency to remain in the mouth in use, thus giving sustained antimicrobial activity and enhanced protection against dental caries and gingivitis.

JP-A-03002113 (Sanpo Seijaku KK) discloses a dentifrice comprising an antimicrobial metal, such as copper, silver or zinc, carried on a zeolite. The dentifrice is stated to be storage-stable.

JP-A-02283312 (Sanpo Seijaku KK) discloses a toothbrush having brush-hairs incorporating a bactericidal metal-carrying zeolite, the metal being carried on the zeolite by ion-exchange. The toothbrush is used for brushing teeth and gums.

EP-A-0251783 (Johnson Matthey PLC) discloses an antimicrobial composition comprising an antimicrobial silver compound deposited on a physiologically inert oxidic synthetic material. The synthetic material is particulate, has an extended surface area, and may be selected from oxides of titanium, magnesium, aluminium, silicon, cerium, zirconium, hafnium, niobium and tantalum as well as calcium hydroxyapatite and barium sulphate. The antimicrobial compound is described as being suitable for topical use, for impregnation of fibrous or absorbent substrates such as bandages or wound-dressings or for impregnation into medical appliances such as catheters.

It has now surprisingly been found that antimicrobial agents of the type disclosed in EP-A-

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0251783 are particularly well-suited to use in oral hygiene compositions. The agents in question show a high degree of substantivity to the mouth, and to the teeth and gums in particular, thus providing sustained  
5 oral antimicrobial action.

According to the present invention there is provided an oral hygiene composition comprising an effective amount of an antimicrobial agent in the form of a particulate non-ion-exchanging support material  
10 combined with a metal source providing antimicrobial metal ions in use.

Preferably, the metal source is a metal compound, preferably a very sparingly soluble metal salt, suitably a silver salt such as silver chloride, since silver ions  
15 show particularly effective antimicrobial action. However, other antimicrobial metals such as copper, gold, platinum and zinc may also be used to good effect. The support material is preferably an inert oxide, preferably an inert metal oxide such as titanium dioxide  
20 (preferably in one or more of the crystalline forms anatase, rutile or brookite, suitably rutile) aluminium oxide, zirconium oxide or magnesium oxide.

Suitably, such antimicrobial agents may be prepared by suspending the support material in an aqueous  
25 solution of a soluble metal compound and reacting this suspension with a compound containing the anion of a desired antimicrobial metal salt. For example, titanium dioxide may be suspended in an aqueous solution of silver nitrate and reacted with silver chloride to  
30 precipitate silver chloride on the titanium dioxide. An example of this process is described in EP-A-0251783 (Johnson Matthey PLC) which is herein incorporated by way of reference.

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Photographic evidence shows that such antimicrobial agents have a high degree of substantivity to the mouth, and tests show that they provide an effective supply of antimicrobial silver ions in use. The agent has particular affinity for carious lesions, cavities and dentinal tubules. The accumulation of the antimicrobial agent in these regions provides a high local concentration of antimicrobial silver ions whilst allowing the overall concentration of such ions in the mouth to be kept quite low, as required to remove any risk of toxicity to the user. The antimicrobial metal ions are thus concentrated where they are needed most, in the carious lesions, cavities and dentinal tubules where the risk of microbially induced decay is greatest.

The antimicrobial agent may be employed alone or in combination with further antimicrobial agents, for instance zinc salts such as zinc citrate and tin salts such as stannous fluoride or stannous pyrophosphate, and organic antimicrobial agents such as bromochlorophene, triclosan and cetyl pyridinium chloride. The latter agents provide excellent short-term antimicrobial action which is, in many respects, complementary to the longer-term action provided by the antimicrobial agents of the present invention.

The antimicrobial metal source may be present in an amount of from 0.5 to 75% by weight of the antimicrobial agent as a whole. Suitably, the amount of the metal source is from 1 to 50%, preferably from 2 to 25% by weight of the antimicrobial agent. The latter range provides a good compromise between the need to provide an antimicrobially effective concentration of free antimicrobial metal ions in use, and the need to keep levels of metal ions low to remove any risk of toxicity and to keep down costs.

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Preferably, the particulate support material has an average particle size of less than 25 micrometres. Suitably, the particle size is between 0.01 and 15 micrometres. Suitably the particles have an open morphology. Preferably each particle comprises an agglomeration of crystallites having open spaces between the crystallites. Suitably the particles are roughly spherical clusters of crystallites. Preferably the particles exhibit some irregularity of shape. Where titanium dioxide is used to provide the crystallites, the primary crystal size will preferably be between 0.005 micrometres and 5 micrometres, preferably between 0.01 micrometre and 1 micrometre, thus allowing the antimicrobial agent to accumulate in carious lesions, cavities and dentinal tubules in use.

Preferably, the support material has a mean surface area of from 1 to 300m<sup>2</sup>/g. It will be understood that a high surface area may be required to support the necessary amount of antimicrobial metal compound, which should preferably be dispersed thinly on the support so as to maximise availability in use.

Suitably, the antimicrobial agent may be included in the oral composition in an amount of from  $1 \times 10^{-5}$  to 5% by weight, preferably from 0.01% to 3% by weight.

The oral composition may be formulated for use in any form of interdental or periodontal treatment and may be in the form, for example, of a dentifrice, mouthwash, toothpowder, chewing gum, lozenge, mouthspray, floss, dental paint, or glass ionomer cement. Use of the antimicrobial material of the present invention in a glass ionomer cement has the advantage of providing X-ray opacity as well as antimicrobial action.

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Such compositions may, as appropriate, contain conventional materials such as, for example, humectants, surfactants, gelling agents, abrasives, fluoride sources, desensitising agents, flavourings, colourings, 5 sweeteners, preservatives, structuring agents, bactericides, anti-tartar agents and anti-plaque agents.

Suitable humectants for use in dentifrice compositions include polyhydric alcohols such as xylitol, sorbitol, glycerol, propylene glycol and 10 polyethylene glycols. Mixtures of glycerol and sorbitol are particularly effective. A humectant helps to prevent dentifrice compositions from hardening on exposure to air, and may also provide a moist feel, smooth texture, flowability, and a desirable sweetness 15 in the mouth. Suitably, such humectants may comprise from about 0-85%, preferably from about 0-60% by weight of the oral hygiene composition.

Suitable surfactants for use in dentifrices, mouthwashes etc. are usually water-soluble organic 20 compounds, and may be anionic, nonionic, cationic or amphoteric species. The surfactant used should preferably be reasonably stable, able to form suds throughout a wide pH range, and able to produce a foam in use.

25 Anionic surfactants include the water-soluble salts of C<sub>10-18</sub> alkyl sulphates (e.g. sodium lauryl sulfates), water soluble salts of C<sub>10-18</sub> ethoxylated alkyl sulphates, water soluble salts of C<sub>10-18</sub> alkyl sarcosinates, the water-soluble salts of sulfonated 30 monoglycerides of C<sub>10-18</sub> fatty acids (e.g. sodium coconut monoglyceride sulfonates), alkyl aryl sulfonates (e.g. sodium dodecyl benzene sulfonate) and sodium salts of the coconut fatty acid amide of N-methyltaurine.



Nonionic surfactants suitable for use in oral compositions include the products of the condensation of alkylene oxide groups with aliphatic or alkylaromatic species, and may be for example, polyethylene oxide condensates of alkyl phenols, ethylene oxide/propylene oxide copolymers (available from BASF Wyandotte Chemical Corporation under the trade name 'Pluronic'), ethylene oxide/ethylene diamine copolymers, ethylene oxide condensates of aliphatic alcohols, long chain tertiary amine oxides, long chain tertiary phosphine oxides, long chain dialkyl sulfoxides and mixtures thereof. Alternatives include ethoxylated sorbitol esters such as those available from ICI under the trade name "Tween".

Cationic surfactants are generally quaternary ammonium compounds having one C<sub>8</sub>-18 alkyl chain and include, for example, lauryl trimethylammonium chloride, cetyl trimethylammonium bromide, cetyl pyridinium chloride, di-isobutylphenoxyethoxyethyl dimethylbenzylammonium chloride, coconutalkyltrimethylammonium nitrite and cetyl pyridinium fluoride. Also useful are benzyl ammonium chloride, benzyl dimethyl stearyl ammonium chloride, and tertiary amines having one C<sub>1</sub>-18 hydrocarbon group and two (poly)oxyethylene groups.

Amphoteric surfactants are generally aliphatic secondary and tertiary amines comprising aliphatic species which may be branched or unbranched, and in which one of the aliphatic species is a C<sub>8</sub>-18 species and the other contains an anionic hydrophilic group, for example, sulfonate, carboxylate, sulfate, phosphonate or phosphate. Examples of quaternary ammonium compounds are the quaternized imidazole derivatives available under the trade name 'Miranol' from the Miranol Chemical Company.

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polymerised resins such as, for example, melamine-ureas, melamine-formaldehydes, urea-formaldehydes, melamine-urea-formaldehydes, cross-linked epoxides, melamines, phenolics, highly purified celluloses such as those  
5 available under the trade name 'Elcema' from Degussa AG, and cross-linked polyesters. Suitably, abrasives are included in an amount of from 0-80%, preferably 0-60% by weight of the oral hygiene composition.

Fluoride sources suitable for use in all oral  
10 hygiene compositions of the present invention include sodium fluoride, zinc fluoride, potassium fluoride, aluminium fluoride, lithium fluoride, sodium monofluorophosphate, acidulated phosphate fluoride, stannous fluoride, ammonium fluoride, ammonium  
15 bifluoride and amine fluoride.

Preferably, the fluoride source is present in an amount sufficient to provide from about 50 ppm to about 4,000 ppm fluoride ions in use. Inclusion of a fluoride source is beneficial, since fluoride ions are known to  
20 become incorporated into the hydroxyapatite of tooth enamel, thereby increasing the resistance of the enamel to decay. Fluoride is also now thought to act locally on the tooth enamel, altering the remineralisation-demineralisation balance in favour of remineralisation.  
25 Inclusion of a fluoride source is also desirable when a polyphosphate anti-calculus agent is included, in order to inhibit the enzymic hydrolysis of such polyphosphates by salivary phosphatase enzymes.

Suitable desensitising agents include, for example,  
30 formaldehyde, potassium nitrate, tripotassium citrate, potassium chloride and strontium chloride (suitably as hexahydrate), strontium acetate (suitably as hemihydrate) and sodium citrate/Pluronic gel.

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Flavouring agents may be added to increase palatability and may include, for example, oils of peppermint, spearmint, wintergreen, sassafras and clove. Sweetening agents may also be used, and these include

5 D-tryptophan, saccharin, dextrose, aspartame, levulose, acesulfam, dihydrochalcones and sodium cyclamate. Typically, such flavouring agents are included in amounts of from 0-5%, preferably from 0-2% by weight of the oral hygiene composition. Colouring agents and

10 pigments may be added to improve the visual appeal of the composition. Suitable colourants include dyes, such as FD & C blue No.1, D & C yellow No.10 and D & C yellow No.3. A suitable and commonly used pigment is pigment grade titanium dioxide, which provides a strong white

15 colour.

Suitably, as described above, the compositions of the invention may include a further antimicrobial agent as a preservative and/or anti-plaque agent. Suitable antimicrobial agents include zinc salts (such as zinc

20 citrate), cetyl pyridinium chloride, the bis-biguanides (such as chlorhexidine), aliphatic amines, bromochlorophene, hexachlorophene, salicylanilides, quaternary ammonium compounds and triclosan. Enzymic systems providing a source of a natural biocide may be used as

25 alternatives to or in combination with the biocides listed. For example, a system comprising lactoperoxidase and glucose oxidase may be used to generate antimicrobial amounts of hydrogen peroxide in the presence of glucose, water and oxygen.

30 The composition may also comprise an anti-calculus agent. Suitable anti-calculus agents include zinc salts such as zinc citrate and zinc chloride and polyphosphates. Suitable pyrophosphates include the sodium and potassium pyrophosphates, preferably disodium

35 pyrophosphate, dipotassium pyrophosphate, tetrasodium

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pyrophosphate and tetrapotassium pyrophosphate. A preferred source of pyrophosphate is a mixture of tetrasodium pyrophosphate and tetrapotassium pyrophosphate. Suitably, the ratio of tetrasodium  
5 pyrophosphate to tetrapotassium pyrophosphate is 0:1 to 3:1, preferably 0:1 to 1:1. Preferably, tetrapotassium pyrophosphate is the predominant species.

The composition may also comprise alcohol. This component is particularly useful in mouthwash  
10 formulations, where it may be used to solubilise components which have low solubility in water.

Particularly suitable oral compositions are those in the form of a mouthwash or toothpaste.

According to a further aspect of the invention,  
15 there is provided a method of cleaning the mouth for cosmetic purposes by oral application of any oral hygiene composition as defined above.

In a further aspect, the invention provides a method of treating or preventing dental caries or  
20 gingivitis by oral application of any oral hygiene composition as defined above.

In a further aspect, there is provided the use of any anti-microbial agent as defined above in the treatment or prevention of dental caries or gingivitis.

25 In a still further aspect, there is provided the use of any anti-microbial agent as defined above in the manufacture of a medicament for the treatment or prevention of dental caries or gingivitis.

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The invention also provides the use of an antimicrobial agent as defined above to provide sustained antimicrobial activity in the mouth.

The nature of the present invention is illustrated  
5 by the following Tests and Examples.

Example 1 (preparative)

A sample of an antimicrobial agent for use in the present invention is prepared substantially as described in EP-A-0261783 (Johnson Matthey PLC).

10 3.55g of silver nitrate is dissolved in 400ml of water at 80°C. 97g of a suitable form of particulate titanium dioxide (having a mean crystallite size of about 250 nm) is dispersed into this solution. 1.4g of sodium chloride (a slight excess) is dissolved in 100ml  
15 of water at 80°C. The sodium chloride solution is then slowly added to the silver nitrate/titanium dioxide suspension with constant stirring. Stirring at a temperature of 80°C is maintained for two hours with light excluded. The temperature is then lowered to 20°C  
20 and stirring continued for a further hour (still excluding light). The suspension is filtered and the silver chloride coated titanium dioxide thus produced is dried and milled, yielding a free-flowing powder containing about 3% silver chloride by weight.

25 Comparative Test A

An antimicrobial agent prepared substantially as described in Example 1 was tested for antimicrobial activity against *Streptococcus salivarius* and *Streptococcus mutans*, which are organisms known to be

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associated with dental caries/gingivitis and against *Candida albicans*

5 A sample of silver chloride coated titanium dioxide was prepared substantially as described in EP-A-0251783 (acknowledged above). The sample was found to have a silver chloride content (as measured by strong acid extraction) of 2.07%, a sodium content of 0.32% and a titanium dioxide content (determined through the residue from acid extraction) of 83.6%

10 Using standard microbiological methods, this sample was placed on an agar plate loaded with test organism. Plates were incubated at 37°C for 48 hours and examined at 24 hours and 48 hours for microbial growth inhibition. By including the sample at different  
15 concentrations it was possible to calculate the minimum inhibitory concentration (MIC) against each organism.

Corresponding tests were carried out on untreated titanium dioxide BP, as a control. Results are shown in Table 1. Where a second figure is shown in the table,  
20 this indicates that a different MIC (as shown) was obtained at 48 hours.

TABLE 1

<u>Organism</u>	MIC (ppm)	
	Untreated TiO <sub>2</sub> (control)	AgCl/TiO <sub>2</sub> (from Example 1)
25 S. Salivarius (NCB 8883)	> 10,000	312 (2,500)
S. Mutans (NCTC 10449)	> 10,000	312 (2,500)
C. Albicans (PHL 239)	> 10,000	5,000

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These results show the activity of the antimicrobial agent of the present invention against organisms known to be associated with dental caries/gingivitis. It will be noted that activity was not  
5 detected in the control.

As noted by Richie and Jones, in Letters in Applied Microbiology (1990) 11, 152-154, the activity shown by the agent of the present invention is probably an underestimate of true activity because of the tendency  
10 of agar and of cysteine and hemin in the culture medium to bind or complex free silver ions. Accordingly, it is to be expected that antimicrobial activity would be considerably greater in vivo.

#### Comparative Test B

15 The anti-plaque activity of the compositions according to the present invention has been demonstrated as follows. Thin strips of aluminium were used as "artificial tooth" surfaces on which plaque, collected from a small number of donors, was grown. Growth was  
20 encouraged by the provision of conditions resembling a normal oral environment (saliva, nutrients, pH and temperature) over a two day period with simulations made of the intake of two meals and of a sleeping, low nutrient period. The aluminium strips (and plaque) were  
25 exposed for one minute on two occasions to a suspension of the composition to be tested with distilled water and fresh saliva, thus simulating evening and morning toothbrushing sessions. Following the second exposure, plaque remaining on the strips after a four hour growth  
30 period and subsequent rinsing was dispersed by ultrasonic vibration. The optical density of the resulting plaque suspensions at 570nm (two replicate readings per strip) was used to estimate the percentage

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CaCl <sub>2</sub>	0.016
MnCl <sub>2</sub>	0.00036

(pH adjusted to 6.8 with HCl)

Medium 2

5	<u>Component</u>	<u>Concentration (g/l)</u>
	CaCl <sub>2</sub>	0.229
	MgCl <sub>2</sub>	0.0403
	NaCl	0.257
	NaSCN	0.105
10	NaF	0.00063
	KI	0.00013
	KHCO <sub>3</sub>	0.5005
	NaHCO <sub>3</sub>	1.68
	KH <sub>2</sub> PO <sub>4</sub>	0.816
15	KCl	0.7455
	Urea	0.193
	Glucose	0.099
	Lactoferrin	0.0054
	Lysozyme	0.132
20	α-amylase	0.38
	Lactoperoxidase	0.002
	Albumin	2.2028

Medium 3

	<u>Component</u>	<u>Concentration (g/l)</u>
25	Tryptone	20



TABLE 2

		Test Solution (antimicrobial agent added at 2 hours)	Control (no antimicrobial agent added)
	<u>Medium 1</u>		
5	pH after 6 hours	6.69	4.44
	pH after 24 hours	4.34	4.10
	OD after 6 hours	0.425	1.74
	OD after 24 hours	0.639	2.092
10	<u>Medium 2</u>		
	pH after 6 hours	7.9	7.51
15	pH after 24 hours	7.83	4.73
	OD after 6 hours	0.434	0.428
	OD after 24 hours	0.32	1.072
20	<u>Medium 3</u>		
	pH after 6 hours	6.91	4.45
	pH after 24 hours	6.64	4.21
25	OD after 6 hours	0.442	1.903
	OD after 24 hours	0.4	2.162

Lower optical densities indicate lower microbial growth. Thus, these results show inhibition of bacterial growth (and associated prevention of reduction in pH in culture media) by use of an antimicrobial agent in accordance with the present invention. Antimicrobial action persisted for at least 24 hours.

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		<u>% w/w</u>
	Sodium fluoride BP	0.05
	Sodium benzoate BP	0.1
	Blue 12401 Anst	0.0006
5	Yellow 2G Anst	0.00055
	Bentonite BP	1
	Mouth rinse flavour (% by volume)	0.1
	Silver chloride coated titanium dioxide (as described in Test A)	0.5
10	Purified water BP	to 100

Formulation Example 3Chewable lozenge

A chewable lozenge is prepared in conventional manner to the following composition:

		<u>% w/w</u>
15	A. Hydrogenated glucose syrup (available under the trade name Lycasin 80/55)	30.0
	Pectin (extra slow set, high-methoxy)	0.6
20	Sorbitol powder (available under the trade name Neosorb)	2.0
	Carrageenan	0.2
	Water	66.1
	B. Citric acid	0.3
	Water	0.3
25	Flavour/colour	0.4
	Silver chloride coated titanium dioxide (as described in Test A)	0.004

Formulation Example 4Chewable tablet (general formulation)

A chewable tablet is prepared in conventional manner to the following composition:

		<u>% w/w</u>
5	Sorbitol (available under the Trade Name Sorbit Instant)	96.9
	Flavour	q.s.
	Colour	q.s.
10	Magnesium stearate (0.5%)	0.5
	Silicon dioxide (0.1%)	0.1
	Silver chloride coated titanium dioxide (as described in Test A)	2.5

Formulation Example 515 Antimicrobial tooth paint base

A tooth paint base is prepared in conventional manner to the following composition:

		<u>% w/w</u>
20	Carboxylated polyacrylate (available under the trade name Surcol 836W)	10.0
	Cellulose acetate	1.0
	Ethanol (96% BP)	88.0
	Silver chloride coated titanium dioxide (as described in Test A)	1.0

Formulation Example 6Chewing gum base

A chewing gum base is prepared in conventional manner to the following composition:

5		<u>% w/w</u>
	Latex (60%)	18.0
	Hydrogenated Rosin Ester	44.0
	Paracumarone ester	7.5
	Candellila Wax	6.0
10	Glyceryl tristearate	2.5
	Ethyl cellulose	2.0
	Calcium carbonate	19.9
	Silver chloride coated titanium dioxide (as described in Test A)	0.1

CLAIMS

1. An oral hygiene composition comprising an effective amount of an antimicrobial agent in the form of a particulate non-ion-exchanging support material combined  
5 with a metal source providing antimicrobial metal ions in use.
2. A composition as claimed in Claim 1 wherein the metal source is a metal compound.
3. A composition as claimed in Claim 2 wherein the  
10 metal compound is a sparingly soluble metal salt.
4. A composition as claimed in Claim 3 wherein the metal salt is a silver salt.
5. A composition as claimed in any one of the preceding claims wherein the support material is an  
15 inert oxide.
6. A composition as claimed in Claim 5 wherein the inert oxide is a metal oxide.
7. A composition as claimed in Claim 6 wherein the metal oxide is titanium dioxide.
- 20 8. A composition as claimed in Claim 7 wherein the titanium dioxide is in the rutile crystal form.
9. A composition as claimed in any one of the preceding claims wherein the antimicrobial agent is employed in combination with a further antimicrobial  
25 agent providing short-term antimicrobial action.

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10. A composition as claimed in any one of the preceding claims wherein the antimicrobial metal source is present in an amount of from about 0.5 to 75% by weight of the antimicrobial agent.
- 5 11. A composition as claimed in Claim 10 wherein the metal source is present in an amount of from about 1 to 50% by weight of the antimicrobial agent.
12. A composition as claimed in Claim 11 wherein the metal source is present in an amount of from about 2 to  
10 25% by weight of the antimicrobial agent.
13. A composition as claimed in any one of the preceding claims wherein the particulate support material has an average particle size of less than about 25 micrometres.
- 15 14. A composition as claimed in Claim 13 wherein the average particle size is between about 0.01 and 15 micrometres.
15. A composition as claimed in any one of the preceding claims wherein the particulate support  
20 material is titanium dioxide having a primary crystal size of from about 0.005 to 5 micrometres.
16. A composition as claimed in Claim 15 wherein the titanium dioxide has a primary crystal size of from about 0.01 to 1 micrometres.
- 25 17. A composition as claimed in any one of the preceding claims wherein the particulate support material has a mean surface area of from about 1 to 300 m<sup>2</sup>/g.

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18. A composition as claimed in any one of the preceding claims wherein the antimicrobial agent is included in the composition in an amount of from about  $1 \times 10^{-5}$  to 5% by weight.
- 5 19. A composition as claimed in Claim 18 wherein the antimicrobial agent is included in the composition in an amount of from about 0.01% to 3% by weight.
20. A method of cleaning the mouth for cosmetic purposes by oral application of an oral hygiene  
10 composition as claimed in any one of the preceding claims.
21. A method of treating or preventing dental caries or gingivitis by oral application of an oral hygiene composition as claimed in any one of Claims 1 to 19.
- 15 22. The use of an antimicrobial agent as defined in any one of Claims 1 to 19 in the treatment or prevention of dental caries or gingivitis.
23. The use of an antimicrobial agent as defined in any one of Claims 1 to 19 in the manufacture of a medicament  
20 for the treatment or prevention of dental caries or gingivitis.
24. The use of an antimicrobial agent as defined in any one of Claims 1 to 19 to provide sustained antimicrobial activity in the mouth.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/01277

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K7/16; A61K9/16		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	CHEMICAL ABSTRACTS, vol. 74, no. 26, 28 June 1971, Columbus, Ohio, US; abstract no. 146414n, SPINKA J. 'Effective substance for tooth pastes and water disinfectants' page 312 ; see abstract & CS 136064	1-6,22, 23
Y	EP,A,0 251 783 (JOHNSON MATTHEY PUBLIC LIMITED) 7 January 1988 cited in the application see the whole document	1-20, 22-24
Y	FR,A,1 550 498 (UNILEVER N.V.) 20 December 1968 see the whole document	1-20, 22-24
-/--		
<p><sup>10</sup> Special categories of cited documents : <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
13 AUGUST 1993	31.08.93 31.08.93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	GAC G.	



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	US,A,3 934 001 (C. A. WATSON) 20 January 1976 see the whole document ----	1-20, 22-24
A	PATENT ABSTRACTS OF JAPAN vol. 015, no. 104 (C-0814)13 March 1991 & JP,A,30 02 113 ( SANPO SEIYAKU KK ) 8 January 1991 cited in the application see abstract -----	1-20, 22-24

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/01277

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 21  
because they relate to subject matter not required to be searched by this Authority, namely:  
See rule 39.1(IV), method of treatment by therapy.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9301277  
SA 74348

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 13/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0251783	07-01-88	AU-B- 599995	02-08-90
		AU-A- 7505487	07-01-88
		DE-A- 3785253	13-05-93
		JP-A- 63088109	19-04-88
		US-A- 4906466	06-03-90
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FR-A-1550498	20-12-68	BE-A- 707693	07-06-68
		CH-A- 518098	31-01-72
		DE-A- 1617926	15-04-71
		GB-A- 1200220	29-07-70
		LU-A- 55049	27-08-68
		NL-A- 6716622	10-06-68
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US-A-3934001	20-01-76	BE-A- 690851	07-06-67
		CH-A- 528269	30-09-72
		DE-A- 1617905	08-04-71
		FR-A- 1504155	
		GB-A- 1166627	08-10-69
		LU-A- 52524	07-06-67
		NL-A- 6617163	08-06-67
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EPO FORM P0079

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82